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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/812,642	03/30/2004	Nikos Pagratis	NEX87/C2	5220

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EXAMINER	
VIVLEMORE, TRACY ANN	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 11/14/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/812,642	PAGRATIS ET AL.	
	Examiner	Art Unit	
	Tracy Vivlemore	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 August 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Any rejection or objection not reiterated in this Action is withdrawn.

Double Patenting

Claims 1-18 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 9-14 of U.S. Patent No. 6,713,616 and claims 2-4 of U.S. Patent No. 6,346,611. This rejection is maintained for the reasons set forth in the office action mailed February 28, 2006.

Applicants traverse the rejections for obviousness type double patenting by arguing that the claims as amended are not obvious variations of the patented claims. Applicants argue that it is not obvious that producing the compounds claimed in the '616 and '611 patents will provide for methods for inhibiting TGFβ2, targeting a nucleic acid ligand to a site in a patient and a method for treating TGFβ2-mediated pathological condition. Applicants further note that a ligand to TGFβ2 may have many uses.

Applicants' arguments have been considered but are not persuasive. The claimed methods are an obvious variation of the patent claims because the patent claims are directed to TGFβ2 nucleic acid ligands and the disclosure of each of the patents specifically contemplates at column 1, "This invention also includes high affinity nucleic acid inhibitors of TGFβ2. The oligonucleotide ligands of the present invention are useful in any process in which binding to TGFβ2 is required. This includes, but is not limited to, their use as pharmaceuticals, diagnostics, imaging agents, and

immunohistochemical reagents." While a ligand to TGFβ2 might have many uses, it would be obvious to one of ordinary skill in the art to use the ligands for the purposes specifically contemplated in the specification of each of the patents.

Response to arguments: Claim Rejections - 35 USC § 112

Claims 1-18 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for use of a nucleic acid ligand to TGFβ2 to inhibit TGFβ2-mediated proliferation of cultured cells, does not reasonably provide enablement for targeting a nucleic acid to a site in a patient, inhibition of TGFβ2 *in vivo* or treatment of a pathological condition mediated by TGFβ2 *in vivo* in any organism using a nucleic acid ligand to TGFβ2. This rejection is maintained for the reasons set forth in the office action mailed February 28, 2006.

Applicant argues that the specification provides teachings relevant to the instant rejection and points to disclosure of the pharmacokinetics of representative nucleic acid ligands in rats, teachings of the isolation of nucleic acid ligands that bind human TGFβ2, teachings of therapeutic compositions and guidance on post-SELEX modifications that improve *in vivo* stability. While the specification does provide guidance regarding these factors, the teachings of therapeutic compositions are directed to general guidance on formulation of compositions but do not teach how to overcome the issues of delivery recognized in the art. The teachings of pharmacokinetics are directed to measuring the time that a nucleic acid ligand remains in the system of an animal but does not address whether any of this ligand enters the cells, one facet of the delivery issue. These studies do not provide any support for a therapeutic use of the disclosed nucleic acid

ligands. The teachings of nucleic acid ligands to human TGFβ2 and post-SELEX modifications similarly do not address the unpredictability of delivery.

With regard to the citation of Opalinska et al., Applicants argue that this reference refers to therapeutic uses of nucleic acids rather than therapeutic uses of nucleic acid ligands. Applicants argue that the difficulties described in Opalinska involved the targeting of a nucleic acid to genomic DNA while the present invention does not involve hybridizing nucleic acids to genomic DNA. While it is correct that the present invention does not require hybridization of the nucleic acid ligand to another nucleic acid, the teachings of Opalinska describe general unpredictability for delivery of nucleic acids. These teachings are not limited to only antisense nucleic acids, but are applicable to delivery of any type of nucleic acids, including nucleic acid ligands. While the nucleic acid ligands of the invention may not act by hybridizing to other nucleic acids, the teachings of Opalinska describe the fate of nucleic acids in cells and are equally applicable to the instant invention.

Priority

No support could be found in the specifications of patents 5,475,096, 5,270,163, 5,660,985 or 5,496,938 for nucleic acid ligands targeted to TGF-β2 or methods of using such ligands. Therefore, the priority date accorded the instant application is June 2, 1995, the filing date of patent 5,731,424. If applicant believes that these patents provide support for the claimed invention, it should be pointed out, with particularity, in any response to this action.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1 and 3-5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gold et al. (US 5,270,163) in view of Tullis (WO 88/09810) and Shah et al. (Journal of Cell Science 1995).

The claims are directed to methods of inhibiting TGFβ2 by administration of a nucleic acid ligand targeted to TGFβ2. In specific embodiments, the nucleic acid ligand is conjugated to PEG that may have a molecular weight of 10-80K or 20-45K. These claims encompass embodiments wherein the TGFβ2 target is in a cell *in vitro* as well as embodiments wherein the TGFβ2 target is in a cell *in vivo*.

Gold et al. teach a method of identifying nucleic acid ligands by a process of *in vitro* selection and amplification. Targets for nucleic acid ligands (see column 13) include growth factors. Nucleic acid ligands are also referred to as nucleic acid antibodies and Gold et al. teach that nucleic acid ligands can be employed in diagnostics in a manner similar to conventional antibody-based diagnostics. Gold et al. also teach at column 9 that nucleic acid ligands have therapeutic uses as sequestering agents, drug delivery vehicles and modifiers of hormone action. Gold et al. do not teach conjugation of a nucleic acid ligand to PEG.

Tullis teaches nucleic acid conjugates comprising an antisense conjugated to a solubility-modifying moiety that may be hydrophobic and imparts amphiphilic character to the final product. At page 7 solubility-modifying moieties are taught as including polyethylene glycol as well as lipophilic compounds such as palmitate, distearylglyceride and cholesteryl. Tullis teaches that the PEG has as many as 500 units, which would have a molecular weight within the ranges recited in the claims. Tullis teaches that the conjugates of the invention find use in drug delivery wherein the amphiphilic nature of the conjugate aids in transport across the cellular membrane.

Shah et al. teach at page 986, column 1 that TGFβ2 is one TGFβ isoform that has a role in cutaneous scarring. Shah et al. further teach on page 987 that inhibition of TGFβ2 through use of a neutralizing antibody reduced inflammatory response in healing wounds and reduced scarring.

It would have been obvious to one of ordinary skill in the art at the time of invention to make nucleic acid ligands taught by Gold et al. in order to target TGFβ2 and

to use these ligands to inhibit a transforming growth factor β2 in cells *in vitro*. It would have been further obvious to one of ordinary skill to conjugate the ligands to a solubility modifying moiety such as PEG as taught by Tullis in order to improve cellular uptake. Gold et al. provide a motivation to use nucleic acid ligands in cells by teaching a method of isolating nucleic acid ligands to any target molecule, suggesting that growth factors are a desired target and by teaching that nucleic acid ligands can act in a fashion similar to antibodies. Shah et al. provide a motivation to target TGFβ2 by teaching its role in cutaneous scarring and that the neutralization of TGFβ2 by an antibody reduces scarring. Tullis provides a motivation to make conjugates of nucleic acids and solubility modifying moieties such as PEG, teaching that such conjugates are readily transported across cellular membrane. One of ordinary skill in the art would have had a reasonable expectation of success in producing a nucleic acid ligand to TGFβ2 because Gold et al. teach that their method is applicable to almost any target. One of ordinary skill in the art would have had a reasonable expectation of success in making a conjugate of solubility modifying moiety and a nucleic acid ligand because Tullis teaches that such oligonucleotide conjugates can be made using routine synthesis methods.

Thus, the invention of claims 1 and 3-5 would have been obvious, as a whole, at the time of invention.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tracy Vivlemore whose telephone number is 571-272-2914. The examiner can normally be reached on Mon-Fri 8:45-5:15.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on 571-272-4517. The central FAX Number is 571-273-8300.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public. For more information about the PAIR system, see http://pair-direct.uspto.gov.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Tracy Vivlemore
Examiner
Art Unit 1635

TV
October 31, 2006